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TYRO3 is a Promising Immune-derived Factor in Diabetic Kidney Disease

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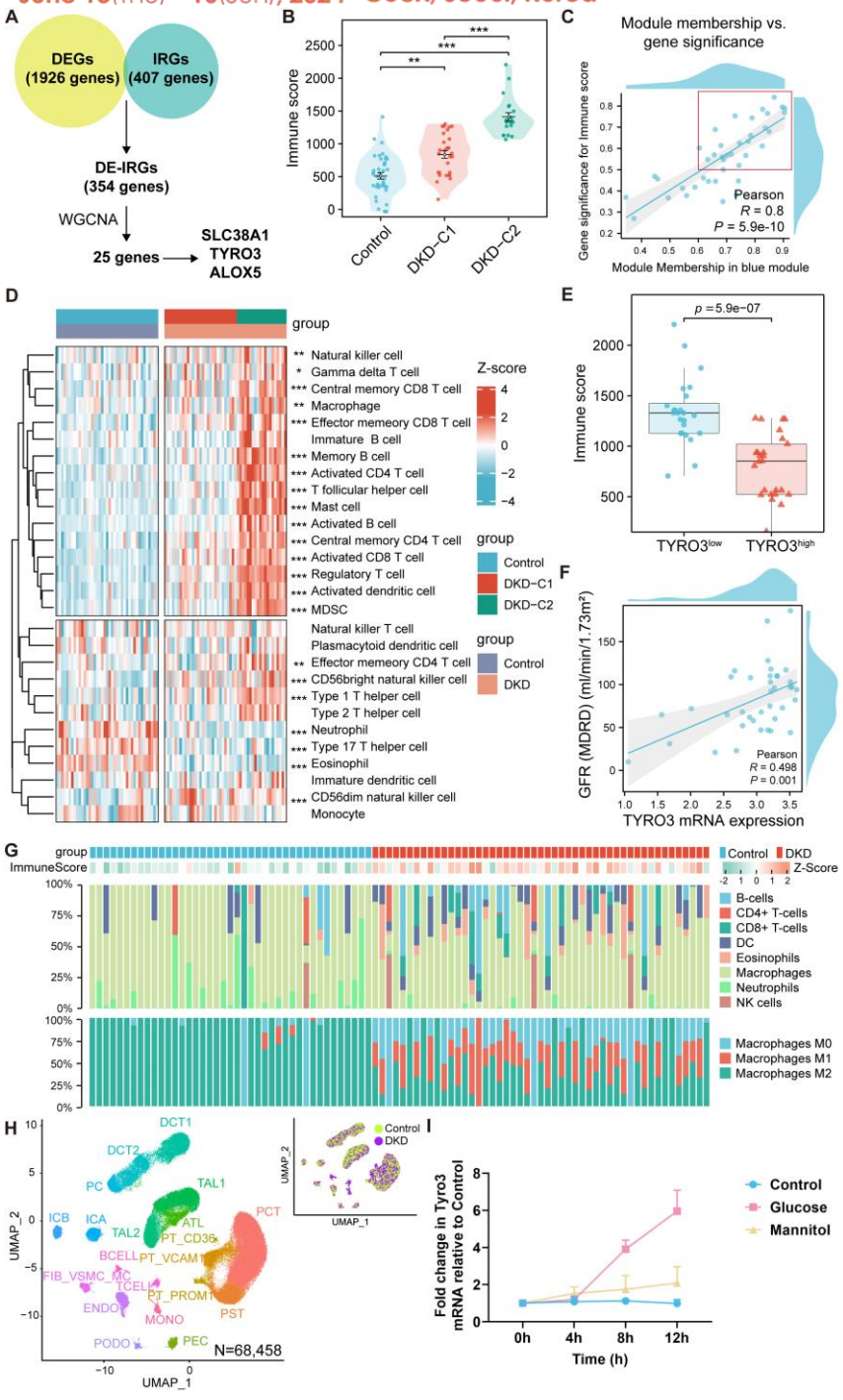
Objectives : Increasing evidence indicates that the contribution of innate immunity to renal inflammation plays a substantial role in the development of diabetic kidney disease (DKD). In this work, we attempted to apply a multi-omics approach with machine learning-based techniques to identify immune-derived new therapeutic targets in DKD.
Methods : In total, we randomly partitioned the independent cohorts into a training set (control: n = 41, DKD: n = 49) and an external validation set (control: n = 20, DKD: n = 41). We attempted Lasso, support vector machine, random forest, supervised machine learning methods. Single-nucleus sequencing data were processed with Seurat v4.0.3. MPC5 cells were treated with the medium containing either normal glucose (5.5 mM), high glucose (30 mM), or high mannitol (30 mM mannitol) for the indicated time intervals. The primer sequences are listed in Table 1.
Results : The optimal prediction model with the highest average C-index (0.8737), and the TYRO3 gene was identified. The high expression levels of TYRO3 subgroup had a significantly lower immune score ($P < 0.001$) (Fig. E). The proportion of M1/M2 macrophages was significantly higher in patients with DKD than in control groups, as confirmed by scRNA-seq results (Fig. G). There was a significantly positive association between TYRO3 expression and eGFR ($R = 0.498$, $P = 0.001$) (Fig. E). As shown in Fig. I, compared with the normal glucose (5.5 mM) group, the increased expression of Tyro3 mRNA in MPC5 cultured with high glucose (30 mM) was obviously time-dependent.
Conclusions : We propose an exploratory approach for inflammatory risk assessment and stratification in DKD. Our results reveal that TYRO3 could be a potential target for regulating immune and inflammatory responses in DKD. Further studies will be required to gain a better understanding of the mechanisms of TYRO3 in the development of renal injury in DKD.

Table 1.jpg

Table 1 Primers used for real-time PCR (5'-3')

Gene	Forward	Reverse
β -actin	GTGACGTTGACATCCGTAAAGA	GCCGGACTCATCGTACTCC
Tyro3	GGAAGAGACGCAAGGAGAC	ATGGGAATGGGGAGACGAC

Table 1.jpg


A
DEGs (1926 genes)
IRGs (407 genes)
DE-IRGs (354 genes)
WGCNA
25 genes
SLC38A1
TYRO3
ALOX5
B
Immune score
Control
DKD-C1
DKD-C2
C
Module membership vs. gene significance
Gene significance for Immune score
Module Membership in blue module
Pearson
R = 0.8
P = 5.9e-10
D
group
Z-score
Natural killer cell
Gamma delta T cell
Central memory CD8 T cell
Macrophage
Effector memeory CD8 T cell
Immature B cell
Memory B cell
Activated CD4 T cell
T follicular helper cell
Mast cell
Activated B cell
Central memory CD4 T cell
Activated CD8 T cell
Regulatory T cell
Activated dendritic cell
MDSC
Natural killer T cell
Plasmacytoid dendritic cell
Effector memeory CD4 T cell
CD56bright natural killer cell
Type 1 T helper cell
Type 2 T helper cell
Neutrophil
Type 17 T helper cell
Eosinophil
Immature dendritic cell
CD56dim natural killer cell
Monocyte
Control
DKD-C1
DKD-C2
Control
DKD
E
p =5.9e-07
Immune score
TYRO3low
TYRO3high
F
GFR (MDRD) (ml/min/1.73m²)
TYRO3 mRNA expression
Pearson
R = 0.498
P = 0.001
G
group
ImmuneScore
Control
DKD
Z-Score
B-cells
CD4+ T-cells
CD8+ T-cells
DC
Eosinophils
Macrophages
Neutrophils
NK cells
Macrophages M0
Macrophages M1
Macrophages M2
H
DCT1
DCT2
PC
TAL1
ICB
ICA
TAL2
ATL
PT_CD36
PCT
BCELL
PT_VCAM1
FIB_VSMC_MC
TCELL
PT_PROM1
ENDO
MONO
PST
PODO
PEC
N=68,458
UMAP_1
UMAP_2
Control
DKD
I
Fold change in Tyro3 mRNA relative to Control
Time (h)
0h
4h
8h
12h
Control
Glucose
Mannitol